PREVALENCE OF OSTEOPOROSIS AND PROXY CLINICAL INDICATORS OF OSTEOPOROSIS IN PATIENTS ON LONG TERM RISPERIDONE

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Dedicated to all the family members of the psychologically disturbed and to the relatives of the mentally ill, who serve them with full patience, dedication and respect.

Dedicated to three of my dear family members who passed away during my post graduation period Bishnu Priya Mohanty, Champa Senapathy & Sarat Chandra Das

DECLARATION

I hereby declare that this dissertation titled “Prevalence of osteoporosis and proxy clinical indicators of osteoporosis in patients on long term Risperidone” is a bonafide work done by me under the guidance of Dr. Deepa Ramaswamy, Professor of psychiatry, Christian Medical College, Vellore. This work has not been submitted to any university in part or full.

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DECLARATION

I hereby declare that the investigations, which form the subject matter of this thesis, **"**Prevalence of osteoporosis and proxy clinical indicators of osteoporosis in patients on long term Risperidone**",** were carried out by **Dr. Jayaprakash R.Ravan**, a bonafide trainee in psychiatry, under my guidance. This has not been submitted to any university in part or in full.

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CONTENTS

INTRODUCTION

Schizophrenia is a chronic and disabling mental disorder associated with abnormalities of brain structure and function (Lewis & Lieberman, 2000). It is characterized by the presence of delusions, hallucinations, disorganized speech and behaviour, with significant impairment in social or occupational functioning (DSM IV, 1994). More than 29 million people suffer from schizophrenia across the globe, of which 20 million live in developing or least developed countries (WHO, 1998). The diagnosis of schizophrenia is based on the patient's self-reported experiences and observed behavior as at present there is no laboratory test available for the diagnosis of schizophrenia.

Schizophrenia is a treatable disorder with the treatment being more effective in its initial stage of illness. (WHO Mental Health Report, 1996). The first-line treatment for schizophrenia is typical or atypical antipsychotic medications and these can significantly alleviate the positive symptoms of psychosis. The second generation/atypical antipsychotics were developed with the hope that they would lead to improve the outcome for individual with schizophrenia in part by reducing both negative symptoms and the burden of extrapyramidal side effects. Although advantage for clozapine has been shown in many studies, it remains unclear whether the other second generation drugs have significant advantages in effectiveness and side effect profile over first generation neuroleptics medication when prescribed in appropriate doses.

The meta-analysis by Davis et al 2003 and by Leucht et al, 2003 supported the advantage of second generation antipsychotic medications in its short term efficacy and relapse prevention. A meta-analysis by Geddes et al 2000 showed a modest advantage

for second generation antipsychotcs in efficacy and extrapyramidal side effects as compared to typical antipsychotic drugs. However according to the exhaustive reviews conducted by the Schizophrenia Patient Outcome Research Team (PORT) 2003 and multi-centric trials CATIE (Clinical Antipsychotic Trial Intervention Effectiveness) funded by NIMH, have concluded there is no significant difference between newer agents as compared to the conventional agents, as far as effectiveness is concerned. The authors conclude that atypical antipsychotics are as effective as the conventional antipsychotics in the treatment of positive psychotic symptoms (Stein D. et al. 2005). However there is some evidence of superiority in the treatment of negative symptoms, mood symptoms, cognitive symptoms and enhanced quality of life by improving tolerability and adherence. Thus taken together, there is evidence to support the use of atypical antipsychotics (excluding Clozapine) as first line treatment agent for schizophrenia. While prescribing atypical antipsychotic medication as first line, clinicians need to be aware of and screen for newer antipsychotic induced adverse effects like weight gain, dyslipedemia, and impaired glucose tolerance hyperprolactinemia and to develop modules to intervene for these conditions.

The antipsychotic drugs induced hyperprolactinemia and related morbidity is a neglected area in clinical practice as well as in research. This secondary hyperprolactinemia may lead to menstrual delay in females, disturbed sexual functioning in males and may cause reduced bone mineral density. (Sauer and Howard, 2002).

Clozapine, Quetiapine and Olanzapine are usually not associated with persistent hyperprolactinemia but may cause transient and mild prolactin elevation. In contrast,

Risperidone and Amisulpride cause a marked and sustained increase in serum prolactin levels. In many studies, Risperidone, a widely prescribed atypical antipsychotic is known to show high propensity to cause hyperprolactinemia compared to typical and other atypical antipsychotic medications.

Risperidone is an atypical antipsychotic, widely available, relatively inexpensive and extensively used in India.

Hyperprolactinemia with antipsychotic medicines can influence bone mineral density. The studies which identified the reduced BMD in patients treated with antipsychotics are preliminary and suffer from small sample sizes and other methodological shortcomings (Haddad et al., 2003). However, they are of concern and need to be studied in people on psychotropic medication.

In this context the current study will estimate the prevalence of deficient bone mineral density and sexual dysfunction in a homogenous group of patients on long-term Risperidone treatment and estimate the correlation between them. As the relationship between antipsychotic use and its effect on BMD is complex, the correct interpretation of relation between Risperidone and BMD needs measurement of 25hydroxy vitamin-D levels, serum calcium, serum albumin, creatinine, serum prolactin and alkaline phosphates.

REVIEW OF LITERATURE

Despite the fact that treatment with prolactin-increasing antipsychotic medication is regularly mentioned as a risk factor for osteoporosis, little is known about the prevalence and the degree of loss of bone mineral density in patients being treated with antipsychotics for psychotic disorders like schizophrenia (Halbreich et al 1995) and bipolar disorder.

Osteoporosis is a disorder of increased bone fragility and low bone mass due to imbalance of osteoblastic and osteoclastic activities with a consequent increase in fracture risk (Johnston et al 1989).

Osteoporosis can be classified into primary and secondary according to its etiology. The term “primary” osteoporosis refers to osteoporosis that results from the involutional loss associated with aging and in women, additional losses related to natural menopause. Osteoporosis that is caused or exacerbated by other disorders or medication exposures is referred to as “secondary” osteoporosis (Lane et al 2006).

The physiology of bone formation, as well as the causes of osteoporosis is complex. In healthy individuals, bone remodelling is a constant, dynamic process, which has three primary functions: repair of micro-damage within the skeleton, maintenance of skeletal strength and regulation of the supply of calcium from the skeleton to maintain serum Calcium. Several circulating hormones such as estrogens, androgens, vitamin D, parathyroid hormone, as well as local factors like insulin-like growth factor, transforming growth factor, parathyroid hormone related peptide, interleukins,

prostaglandins, tumour necrosis factor and osteoprotegrin ligands (Lindsay et al., 2001) regulate bone remodelling.

Osteoporosis is a serious public health issue, affecting up to 1 in 2 women and 1 in 5 men over the age of 50 years. The common osteoporotic fractures occur at the spine, wrist and hip (Richard Keen, 2007). Osteoporosis is a prevalent condition that affects 1 in 4 women and 1 in 8 men in general population in Canada. (Clarene et al, 2004). One out of every two women and one in eight men over 50 years of age will have an osteoporosis-related fracture in their lifetime. The mortality rate associated with osteoporosis is substantial; for example, out of 80,000 men who suffer from a hip fracture each year, one-third die.

Also, decreased BMD and resulting fractures place a significant financial burden on the health care system (NIH Osteoporosis Overview, 2000).

Gold standard test to evaluate osteoporosis

Bone strength is dependent on bone mineral density (BMD) and bone quality. BMD is the most readily accessible and quantifiable marker of bone strength and is often used as a predictor of fracture risk (Clarene H et al., 2004). Radiological measured bone mineral density (BMD) is an index of bone mass and is calculated by dividing the mineral content by the area or volume of bone scanned. Techniques commonly used are dual-energy X-ray absorptiometry and computed tomographic scanning.

Dual-Energy X-ray Absorptiometry (DXA) is at present considered to be the gold standard in measuring the BMD at the hip or spine. Additionally, it can also be used to measure the total amount of mineral in the whole skeleton or forearm. Hip BMD predicts risk of fractures at all other sites (11). It is usually unaffected by degenerative arthritis when compared with spine BMD. Spine BMD measures vertebrae L1 through L3 or L4. Vertebral bodies are largely made of trabecular bone that, because of its high ratio of remodeling surface to bone volume, is more sensitive to the effects of hormones and drugs than is cortical bone. Therefore, spine BMD tends to change, more in response to some medical conditions, such as glucocorticoid excess, and to treatments than does BMD of other sites. On the other hand, standard spine BMD, measured in the anteroposterior direction, includes mineral in the posterior elements and facet joints as well as the abdominal aorta, none of which contribute to the strength of the vertebral body. Consequently, spine BMD is increased by degenerative arthritis and, for this reason, may increase in some individuals after the age of 65 years rather than decrease when compared to other BMD measurements.

T and Z scores

Densitometers report T and Z scores that are specific to the patient's sex, and some manufacturers report values compared with those of patients of the same race. A Z score is the number of Standard Deviation (SD) s below or above the mean BMD value for people of the same age. A Z score of 0 means that the patient has a value that is exactly at the mean for her age. A Z score of minus 2.0 means that the patient has a BMD at that site, by that method, that is 2 SDs below the mean BMD value of others the same age.

In contrast, a T score is the number of SDs (standard deviations) below the mean BMD for young (25- to 45-year-old) adults. A T score of 0 means that the patient has a BMD value that is exactly at the mean for young adults. Both of these variables rely on SD for the measurement. An SD represents the normal variability in a measurement in a young normal population—the distance between the 5th and 95th percentile of a group covers about 4 SDs. Standard deviations vary from technique to technique and among various reference populations that are used to define normal values. For hip and spine BMD, 1 SD corresponds to about 10% to 15% of the mean value for young adults.

A T score of minus 2.5 means that the patient has a BMD value at that site and by that method that is 2.5 SDs below the mean. Because BMD declines with age, T scores are consistently lower than Z scores after about age 40 years, and the difference increases with age. Since the relationship between decreasing bone density and increasing risk of fractures is a continuous one, there is no threshold or cutoff value to distinguish low- and high-risk people.

WHO criteria for Osteoporosis & Osteopenia

The World Health Organization has defined osteoporosis as a bone density with a T score of minus 2.5 or less and osteopenia as a bone density T score between minus1.0 and minus 2.5. This cut-off has no inherent biological meaning as it was created to allow comparisons of the prevalence of osteoporosis in different countries and was not intended (initially to be used) to make treatment decisions.

The diagnosis of osteoporosis according to BMD can be confusing at times, if 2 or more sites are measured, patients will sometimes have a T score of minus 2.5 or less

and so-called osteoporosis at one site and above that level at other sites (14). Some experts and guidelines

Consider a T score at or less than minus 2.5 at the femoral neck or total hip to be the gold standard for the diagnosis of osteoporosis. Others prefer to diagnose osteoporosis if the T score at either the hip or spine is at or below minus 2.5; the latter approach designates more women as having osteoporosis who will, on average, have a somewhat lower risk of fracture. The upper cutoff, a T score of minus 1.0, was also chosen arbitrarily to indicate women whose bone density was below normal for young adults.

The BMD value can be used to predict the risk of later fractures and the risk of fracture approximately doubles with each standard deviation of decrease in age-adjusted mean BMD (Genant et al., 1999).

Mechanism of bone loss

Hyperprolactinaemia is associated with reduced bone mineral density. This is mediated by the inhibition exerted by dopamine on the hypothalamic–pituitary–gonadal axis and the resulting hypogonadism.

In women, a chronic elevation of prolactin levels induces inhibition of the hypothalamic secretion of luteinizing hormone-releasing hormone. This, in turn, lowers levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which regulate gonadal steroid production and release. The principle gonadal steroid, estrogen inhibits osteoclasts, which are responsible for bone resorption, and stimulate osteoblasts

that mediate bone formation. Hence, estrogen deficiency may reduce bone density in women by increasing osteoclastic activity and reducing osteoblastic formation. (Halbreich et al., 2003). Estrogen may also play an important role in determining the life span of bone cells by controlling the rate of apoptosis. Hence, in low estrogen states, the lifespan of osteoblasts may be decreased and the longevity of osteoclasts increased. In adolescents and young women, sustained production of estrogen is essential for the maintenance of bone mass and persistent estrogen deficiency secondary to prolactin elevation causes significant bone loss. (Coss et al, 2000).

In males, testosterone deficiency has been shown to be associated with osteopenia (Halbreich U, 1996).

Other minor mechanisms are mentioned in literature. Elevated levels of parathyroid hormone (PTH)-related peptide (PTHrP), secondary to hyper- prolactinemia, can cause bone mineral density changes (Raisz et al., 2003). Reduced estrogen can influence the activity of interleukins, which are known to influence bone dynamic homeostasis (Halbreich et al., 1996).

Risk factors for low MBD:

Major risk factors for low BMD	Minor risk factors for low BMD
Alcohol and drug abuse	Rheumatoid arthritis
Heavy smoking	Past history of clinical hyperthyroidism
Immobility	Chronic anticonvulsant therapy
Reduced exposure to sunshine resulting in vitamin D def	Low dietary calcium intake
Polydipsia and dietary deficiency	Excessive caffeine intake
Systemic glucocorticoid Rx >3/12	Chronic heparin therapy
Vertebral compression fracture	Weight loss >10% of weight at age 25
Fragility fracture after age 40	Body Weight <57kg

(Clarene Ho et al 2004; Cantor-Graae E et al 2001; Kavanagh DJ, 2002 and DeLeon J 1994)

Prolactin physiology and regulation

Prolactin is secreted in a pulsatile manner by the anterior pituitary gland. There are 13 or 14 peaks per day, with an inter-pulse interval of about 95 min. The upper limit of unstipulated prolactine levels in men and women varies between laboratories, ranging between 350 mU/l and 550 m U/l. (Veldhuis and Johnson, 1988). Hypothalamic dopamine is the predominant prolactin-inhibiting factor. Released into the portal hypophyseal circulation it binds to D2 receptors on lactotroph cells. Stimulation of D2 receptors has inhibitory effects on prolactin gene transcription, synthesis and release.

Serotonin (5-HT) has a stimulatory role in prolactin regulation mediated through 5-HT1A and 5-HT2 receptors. Estrogens can modulate prolactin secretion by inhibiting hypothalamic dopamine synthesis, reducing the number of pituitary D2 receptors, enhancing prolactin gene transcription and synthesis.

The hyperprolactemia can be clinically manifested as amenorrhea, cessation of normal cyclic ovarian function in female and hypospermatogenesis in male (Petty, 1999).

Literature on Hyperprolactemia and its secondary complication

In women with pituitary adenoma and hyperprolactinemia had 17% decrease in cortical bone and 25% of trabecular bone. (Klibanski, 1980; Cann, 1984; Koppelman, 1984; Schlechte, 1987). In men hyperprolactinemia resulting from prolactin-secreting pituitary tumours also caused hypogonadism and osteoporosis. Greenspan demonstrated significant loss of BMD in forearm and vertebrae in men with hyperprolactinemia (Greenspan et al, 1986).

Hyperprolactinemia and Amenorrhea

Hyperprolactinemia hypogonadal women with secondary amenorrhea resulting from low estrogen production were found to have significantly lower BMD than hyperprolactinemic women who maintained sufficient estrogen levels to retain menses. The duration of amenorrhea was positively associated with severity of BMD loss.

Forty-two percent of hyperprolactinemia women who remained amenorrhic for a period of 1.7 + 0.2 years exhibited BMD loss more than two standard deviations below the control mean (Biller et al., 1991).

Antipsychotic induced Hyperprolactinemia

All conventional antipsychotic drugs cause dose dependent blockade of D2 receptors on lactotroph cells removing the main inhibitory influence on prolactin level and causing hyperprolactinemia. This is defined as a level above the upper limit of normal (>24.20 ng/ml for females and >18.77 ng/ml for males). Elevation of prolactin levels occurs within a few hours of treatment initiation and persists with long-term treatment. (Smith, 2002). Women have significantly greater prolactin elevations than men during chronic antipsychotic treatment with equivalent doses. (Wode-Helgodt et al., 1977; Kuruvilla et al., 1992; Smith et al., 2002).

When oral antipsychotic therapy is discontinued, baseline prolactin levels may take up to 3 weeks to return to the normal range depending on the half-life of the drug and its metabolites as well as storage in fatty tissues (Turkington, 1972). In the case of depot medication, normalization may take as long as 4-6 months (Wistedt B., Wiles D. & Kolakowska T., 1981).

Recent research in the field of antipsychotic induced osteoporosis

In a cross-sectional study of 402 (147 female + 255 males) patients in whom prolactin levels were measured after a minimum of 3 months' treatment with conventional anti-

psychotics or Risperidone (Kinon and Glimor, 2001), the prevalence of hyperprolactinemia among women of reproductive age (n=90) was 65.6% (mean serum prolactin=69.0 ng/ml), and among postmenopausal women (n=51), it was 45.1% (mean serum PRL=49.0 ng/ml). The prevalence of hyperprolactinemia across all males (n=255) was 42.4% (mean serum PRL= 32.4 ng/ml). The prevalence of hyperprolactinemia among females taking Risperidon (N=42) was 88% versus 47.6% of those taking conventional antipsychotic drugs (N=105), with 48% of those females of reproductive age on Risperidone experiencing abnormal menstrual cycles (secondary amenorrhea, oligomenorrhea, or polymenorrhea). Thus hyperprolactemia was more in female (as compared to male) with Risperidone (as compared to conventional antipsychotics) in the reproductive age group (than post menopausal group).

Antidepressants with serotonergic activity, including selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and some Tricyclic antidepressants, anti epileptic mood stabilizer can cause modest elevations of prolactin levels.

When these drugs are given as monotherapy patients have reported symptoms of hyperprolactinemia, but such reports are rare. In patients whose prolactin secretion is already stimulated by antipsychotic drugs, SSRI or Mood stabilizer have the potential to elevate prolactin levels above the threshold for ovarian dysfunction and galactorrhoea or to worsen existing symptoms.

Studies of bone density in psychiatric patients

In women exposed to antipsychotic medication bone density has been assessed in few studies.

Ataya's study assessed only ten premenopausal women who had been treated with antipsychotic drugs for an average of 10 years and had developed amenorrhea or oligomenorrhoea. DEXA Scan was taken for whole spine and head and neck of femur. Data was compared with age and gender related normative values from a large database.

The study showed BMD was reduced by about 12% at three sites of the femur, but not in the spine. Ataya *et al (*1988) talk about the antipsychotics induced bone mineral density changes in premenopausal patients who are clinically symptomatic. However this was a very small sample size and clinically asymptomatic patient who might have BMD changes were not included.

Halbreich *et al* (1995) found significantly reduced BMD values in the lumbar spine in a group of women treated with antipsychotic, antidepressant and mood-stabilizing medication, either alone or in combination. The finding of this study suggested for the first time loss of bone mineral density in the lumbar spine. However the limitation of the study was the heterogeneous composition of the study group.

Hummer et al (2005) in a cross-sectional study used dual x-ray absorptiometry to determine bone mineral density of 75 inpatients and outpatients suffering from schizophrenia. All patients had been treated with antipsychotics for at least 1 year, and only patients between the ages of 19 and 50 were studied to exclude patients with age-related idiopathic osteoporosis. In men, but not women, with schizophrenia, bone mineral density was significantly lower than normal in the lumbar region. A comparison of loss of bone mineral density in male and female patients showed significant differences between the sexes. Bone mineral density showed a negative correlation with negative symptoms and Positive and Negative Syndrome Scale total score and a positive correlation with 25-hydroxy-vitamin D3 levels and body mass index in male patients.

In female patients, a positive correlation between body mass index and bone mineral density was found. Exposure to prolactin-increasing antipsychotic was not related to bone mineral density.

In a study comparing the BMD changes between prolactin sparing and prolactin rising antipsychotic (O'Keane, Meaney et al., 2005) 64% of patients on prolactin rising antipsychotic had decreased BMD.

In a review of bone mineral changes in male schizophrenic patients estimated prevalence of osteopenia ranging from 40-72% compared to controls (Jonathan, Meyer David et al., 2006).

Meaney and O'Keane, (2007) on an interventional study compared BMD alterations over a period of 1 year in patients maintained on either prolactin-raising (e.g. risperidone, amisulpride or depot anti-psychotics) or prolactin-sparing (Olanzapine) anti-psychotics. Pre-menopausal females (n=38) with a diagnosis of schizophrenia, who had received exclusively either prolactin-raising (n=25) or prolactin-sparing (n=13) anti-psychotics during their treatment history, had clinical, endocrine and bone marker assessments performed at baseline and every 3 months for a period of 1 year. BMD was measured by DXA scan at baseline and at 1-year follow-up. Patients from both groups either received specific interventions (n=16) or no interventions (n=16) to improve bone density. Women taking prolactin-raising anti-psychotics and not receiving specific interventions to improve bone density had evidence of ongoing bone demineralization over a year; whereas women taking prolactin-sparing anti-psychotic drugs had a modest overall increase in BMD. This is the only interventional study available in literature as per our knowledge.

Role of Vitamin D status in relation to BMD

Bone mineral density is also influenced by vitamin D status. Bone mineral loss in vitamin D insuffiency is caused by more than one mechanism. The secondary hyperpathyroidism resulting from low vitamin D has a detrimental effect on bone mineral density. Low serum 25 (OH) vitamin D concentration is the hallmark of vitamin deficiency. A level of more than 30 ng/ml is considered adequate (Holick et al, 1995). The Indian subcontinent, situated between 8.4_ N and 37.6_ N latitude, has adequate sunshine and UV B rays (290–315 nm) reaching the earth's surface throughout the year (40). Therefore, it has been presumed that Indians are vitamin D

sufficient. Goswami R et al in a study on healthy Indians has suggested a high prevalence of subnormal 25 (OH) D concentrations. It has been demonstrated in similar other studies from India (Paul et al 2008, Goswami et al 2008)

Role of Vitamin D status in relation to psychiatric morbidity

Vitamin D not only is integral to maintaining bone health, but it also plays a role in several other biochemical mechanisms within the human body. 15 years ago, Professor Walter E. one of the great pioneers in vitamin D research, predicted a substantial role for both bright light and vitamin D in psychiatry. In 1999, study conducted by Hollis B showed that 100,000 IU of vitamin D given as a one time oral dose improved depression scales better than light therapy in a small group of patients with seasonal affective disorder. German authors also found healthy controls had an average serum 25(OH) D of 46 ng/L while depressed subjects had 37 ng/L. Most recently, a direct correlation was found between 25(OH)D levels and mental health scores in a group of healthy, elderly adults, although 1,000 IU of cholecalciferol per day did not improve mental health scores of these highly-functional subjects and this may be attributed to inadequate dosing of Vitamin D(less than 2000IU per day The probable mechanism related to vitamin D supplementation and improvement of depression is that vitaminD rapidly increases the in-vitro genetic expression of tyrosine hydroxylase (the rate-limitin enzyme for the catecholamine biosynthesis) by threefold. Vitamin D also increases the expression of tyrosine hydroxylase gene in adrenal medullary cells.

Evidence suggests that vitamin D may help mood but that evidence is not conclusive. The above positive studies used vitamin D to treat seasonal affective disorder, not

major depression. There is enough biological evidence to suggest an important role for vitamin D in brain development and function. However, direct effects of vitamin D inadequacy on cognition/ behaviour in human or rodent systems appear to be subtle.

The vitamin D hypothesis of schizophrenia is a recent concept bringing together old observations on environmental risk factors and new findings on the neurodevelopmental effects of vitamin D. Candidate genes related to the vitamin D endocrine system have not yet been fully explored for this purpose. The coexistence of vitamin-D-dependent-rickets type II with alopecia (VDDR IIA) and different forms of psychosis in the same inbred family has provided us with an opportunity to investigate the presumed relationship.

AIMS AND OBJECTIVES OF STUDY

The aims of the study:

1. To estimate the prevalence of osteoporosis in patients taking Risperidone for more than 1 year.

2. To study the prevalence of hyperprolactinemia and to estimate the association between hyperprolactinemia with sexual dysfunction.

3. To study the drug dose and various bone mineral parameters and their influence on BMD.

4. To estimate the association between decreased BMD and erectile dysfunction in males or amenorrhea in females.

METHODS AND METHODOLOGY

Subjects for screening were be obtained by three methods. First, charts of all outpatients attending the psychiatry review clinics – Monday to Thursday, 2 to 5 pm - were checked at the MRD, by the principal investigator (PI), before distribution. 250 to 350 patients are seen on each day. Second, all clinical staff were informed of the study and requested to refer suitable subjects. Third, all inpatients will be screened. Screening was conducted on the basis of recorded data from the chart.

Screening would include adults between the ages of 18 and 50 years, and who have been on Risperidone as the sole antipsychotic, for at least 12 months. Exclusion criteria included the drugs other than Risperidone, which cause hyperprolactemia and the conditions known to be associated with osteoporosis, the outcome of interest.

The PI, in the appropriate language, and using lay terms, explained the nature of the study to the potential subject and the relative, when present. The format for this is attached as Appendix I. The PI speaks English, Hindi, Bengali, Oriya and Tamil with sufficient fluency.

Written informed consent was obtained.

The bone mineral density of the subject was assessed with dual X-ray Absorptiometry (DXA). This was done at CMCH and the PI made the appointment at the patient's convenience.

The interpretation of the findings and the diagnosis and grading of osteoporosis was done by the staff of the department of endocrinology. They did not have access to the clinical details of interest in the study.

Data on socio-demographic variables, medication details and putative proxy clinical indicators (amennorhea in women and erectile dysfunction in men) were also be obtained using a specially designed proforma.

64 subjects will be recruited into the study.

The biostatistician has been consulted. Sample size calculation has been done on the basis of prevalence reported in previous studies.

Inclusion Criteria

- Age between 18 and 45 years.
- Patient on Risperidone as the only antipsychotic drug for at least for 12 months
- Subjects giving written informed consent

Exclusion Criteria

- Patients with Alcohol dependence syndrome or Anorexia Nervosa.
- Patients on combination of antipsychotic medications.
- Patients on other drugs which can cause hyperprolactinaemia, (Sodium Valproate, Carbamazepine, Tricyclic antidepressants, Specific Serotonin Reuptake Inhibitors, and oral contraceptive pills)

- Non-ambulant patients.
- Pregnant or lactating women.

Evaluation

Patients who fulfilled the eligibility criteria were selected for the study. The following parameters were assessed.

1. Clinical and demographic profile

– All patients were asked for their demographic details, duration of untreated psychosis, past history of exposure to antipsychotic medication, duration of treatment with risperidone, and other psychotropic drug given with risperidone, history of bone pains, fractures and proximal muscle weakness. From the patient charts, the details regarding the Axis –I diagnosis and other co-morbid conditions were obtained.

2. Biochemistry

The following **biochemical parameters** were assessed.

Fasting blood samples were collected for the assessment of serum calcium, phosphate, alkaline phosphatase, albumin, creatinine and 25 hydroxy Vitamin D.
These parameters were measured in HITACHI 911 model auto analyzer, which is a fully automated and computerized microanalyser (Boehringer Mannheim).

Calcium

– Calcium forms a violet complex with O-cresolphthalein complexone in an alkaline medium. The violet colour medium is measured photometrically at 570 nm. [Normal range: 8.3 to 10.5 mg per deciliter].

Phosphate

– Inorganic phosphorus reacts with ammonium molybdate in sulphuric acid solution to form ammonium phospho molybdate, which is blue in colour and measured at 340 nm [Normal range: 2.5 to 5.3 mg per deciliter].

Alkaline Phosphatase

– The activity is measured kinetically by the formation of paranitrophenol from paranitrophenylphosphate. Alkaline phosphatase hydrolyses p-nitrophenylphosphate to paranitrophenol, which is measured photometrically at 415 nm [Normal range: 40 – 125 U per litre].

Creatinine

– Creatinine forms a coloured complex with picrate in alkaline solution. The rate of formation of this complex is measured at 505 nm. [Normal range: 0.5 – 1.4 mg per deciliter].

Albumin

When bound with bromocresol green, albumin exhibits change in absorbance at 600 nm, which is the result of formation of a green coloured albumin dye complex. The intensity of the colour is proportionate to the concentration of Albumin [Normal range: 3.5 – 5.0 gm per deciliter]

25 OH vitamin D (vitamin D)

It was measured using electrochemiluminiscence method (Roche diagnostic, Indianapolis, US). This assay uses a polyclonal antibody directed against 25-OH vitamin D3. The analytical sensitivity is 4ng/ml. It has a coefficient of variation of 6.6 to 9.9% at low and high levels. Vitamin D levels more than 30 ng/ml was considered sufficient. Levels between 10-30ng/ml was considered insufficient and levels <10ng/ml was considered vitamin D deficient.

Prolactin

Serum prolactin was measured using chemi luminescent assay in Immulite 2000 Hyperprolactinemia was defined as the level of serum prolactin of >24.20 ng/ml for females and >18.77 ng/ml for males. This assay had analytical sensitivity of 0.16%

3. Bone densitometry

DXA scan: BMD was assessed by using the Hologic Machine (QDR 4500; Hologic, Inc., Waltham, MA, USA) at lumbar spine and femoral neck. Reference population was normal Caucasians (manufacturer's database). Precision was 2 percent at both the measured sites (spine and neck of femur).

SAMPLE SIZE CALCULATION

Sample size was calculated using the formula: $n=4pq/d^2$ A sample size of 64 was required to find a prevalence of 20% ± 10 at 95% confidence

STATISTICS

An Independent T test was used to compare the means of two continuous variables if they were normally distributed and nonparametric tests were used if their distribution were not normal. Chi square or Fisher exact test was used when variables were categorical. A correlation between 2 continuous variables was done using Pearson's correlation. Logistic regression was done to assess the effect of multiple variables on bone mineral density and osteoporosis. Statistical analysis was done using the SPSS 11 software package

RESULT

Table 1: Demographic data

Variables	Subgroups	Mean (SD)
Age groups	18-45	29.45 (6.56)
Gender	Female Male	32 (49.2%) 33 (50.8%)
Religion	Hindu Christian Muslim	60 (92.3%) 4 (6.1%) 1 (1.5%)
Diagnosis	Schizophrenia Psychotic Bipolar Schizoaffective Acute psychosis	38 (58.5%) 23 (35.4%) 2 (3.1%) 2 (3.1%)
Past history of antipsychotic exposure	P/H of ASD exposure Nil	18 (27.7%) 47 (72.3%)
Current combination of treatment	Only on risperidone Risp+Pacitine Risp+Lithium Risp+LI+ Pacitine Risp+BZD Risp+Li+BZD	18 (27.7%) 27 41.5% 11(16.9%) 5 (7.7%) 3(4.6%) 1(1.5%)

The demographic data is explained in Table 1. Sixty five patients with mean age of 29.45 year (6.56) fulfilled the inclusion criteria and were included in the study after obtaining informed consent. 60 (92.3%) of the subjects were Hindus and 5 (7.7%) belonged to Muslim or Christian community. An ICD 10 diagnostic criterion for schizophrenia was met by 38 (58.5%). The remainders were diagnosed to have either psychotic bipolar disorder (35.4%) or acute psychosis (3.1%) or schizoaffective disorder (3.1%).

Within the total subject group, 18 (27.7%) of the patients were only on Risperidone where as the others were on the combination of Risperidone with other medications - Risperidone with Lithium were 11 (16.9%); Risperidone plus Trihexyphenidyl 27 (41.5%); risperidone plus Lithium with Trihexyphenidyl 5 (7.7%) and Risperidone with benzodiazepine 4 (6.1%).

Table 2: Comparison of Demographic and clinical data in both genders

Variables	Total N=65	Female N=32	Male N=33	P value
Age	29.45 SD 6.56	28.84 SD 6.59	30.06 SD 6.53	0.458
Religion	Hindu 60 (92.3%) Others 05 (07.7%)	28 (87.5%) 04 (12.5%)	32 (97.0%) 01 (03.0%)	0.197
Occupation	Job 54 (83.1%) Nil 11(16.9%)	28 (87.5%) 04 (12.5%)	26 (78.8%) 07 (21.2%)	0.511
Diagnosis	Schiz: 38 (58.5%) Bpad/scizoaff: 27(41.6%)	21 (65.6%) 11 (34.4%)	17 (51.5%) 16 (48.5%)	0.450
Comorbid axis I	Present: 3(100%) Nil 0	32 (100%) 00	30 (91.9%) 03 (09.1%)	0.238
Past H/O antipsychotic	Present: 18 (27.7%) Nil: 47 (72.3%)	10 (31.3%) 22 (68.8%)	8 (24.3%) 25(75.7%)	0.587
Dose of risperidone	Dose of risperidone 0-4mg Dose of risperidone 4.5-10.5mg	17 (53.1%) 15 (46.9%)	19 (57.6%) 14 (42.4%)	0.805

Table 2 shows that this group consists of thirty two women (49.2%) with mean age of 28.84 (6.59) and thirty three men (50.8%) with mean age of 30.06 (6.53) There was no significant difference between the male and female groups in terms of religion, occupation, co-morbid Axis -I diagnosis or past history of exposure to other antipsychotics.

Table3: Comparision of clinical profile across male and female groups

Variables	Mean with SD	Female N=33	Male N=32	Odd ratio/P value
Age	29.45 (6.56)	28.84 (6.59)	30.06 (6.53)	0.458
Age of onset of psychosis	24.38 (5.51)	24.31 (5.48)	24.45 (5.63)	0.92
Duration of untreated psychosis	7.43 (12.048)	7.00 (10.68)	7.85 (13.39)	0.779
Average Dose of Risperidone for last 1 year	4.68 (1.778)	4.53 (1.79)	4.82 (1.77)	0.520
Duration of treatment with Risperidone	32.63 (21.468)	29.94 (17.01)	35.24 (25.04)	0.323

Table 3 shows comparison between men and women on additional clinical variables. It was found that there was no significant difference in terms of age of onset of psychotic illness, duration of untreated psychosis, average dose and mean duration of treatment with risperidone.

Table 4.1: Comparison of the biochemical variables across gender

Variables	Female mean (SD)	Male mean (SD)	P value
Alk phos	84.12 (22.63)	81.39 (26.42)	0.656
Phosphorus	3.66 (0.64)	3.74 (0 .47)	0.583
BMI	27.7 (5.7)	24.49 (5.22)	0.026

The biochemical parameters were compared amongst the sub groups of both female and male and it was observed that there was no significant difference between the male and female groups in terms of mean level of serum alkaline phosphatase, serum calcium, phosphorous or serum vitamin D. However, there was a significant difference between female and male groups in terms of body mass index ($p = 0.026$) and serum prolactin level $p < 0.0001$.

Table 4.2: Comparison of Hyperprolactinemia and Vitamin D deficiency across gender

Biochemical level	Female N=33	Male N=32	P value	Odd ratio
Hyperprolactemia	27 (84.4%)	26 (78.8%)	0.103	1.454(0.409-5.165)
Normal Prolactin	05 (15.6%)	07 (21.2%)		
Normal Vitamin D	0 (0%)	03 (9.30%)	0.24	2.47 (0.82-7.46)
Either Vitamin D deficient or insufficiency	31(100%)	29 (91.7%)		

Hyperprolactinemia is defined as the level of serum prolactine of >24.20 ng/ml for females and >18.77 ng/ml for males. In this study, the prevalence of Hyperprolactemia in female was found to be 27 (84.4%) and in males 26 (78.8%). The odds ratio estimation showed female were 1.4 times at more risk of Hyperprolactinemia as compared to males.

Out of the 65 subjects taken in to the study, 2 women and one man (4.6%) were missed out on Vitamin D level assessment. Of the rest, 60 (92.3%) had vitamin D deficiency (n=20, 30.8) or vitamin D insufficiency (n=40, 61.5%). Only 2(3.1%) of the subjects had normal serum vitamin D level (>30 ng/ml). The comparison between the gender groups in relation to Vitamin D deficiency and Vitamin D non-deficiency did not show any significant difference.

Bone mineral density measure in neck of the femur

40% of subjects had BMD abnormalities in the neck of femur. 2 subjects had osteoporosis (3.09%) and 24 (36.91%) had osteopenia. Both subjects with osteoporosis were male. Overall, 14 (42.5%) of the men and 12 (37.5%) of the women had reduced bone mineral density values at neck of the femur.

Table 5: Clinical and demographic parameters compared for neck of the femur

Variables	N (%)	Normal BMD N =39	Osteoporosis/penia N=26	P value
Gender	Female: 32 (49.2%) Male: 33 (50.8%)	20(51.3%) 19 (48.7%)	12 (46.2%) 14 (53..8%)	0.801
Diagnosis of the patient	Schizophrenia: 38 (58.5%) BPAD /SA dis: 27 (41.6%)	24 (61.5%) 15 (38.5%)	14 (53.8%) 12 (46.2%)	0.612
Co –morbid Axis I diag.	No Comorbid dis: 55 (84.6%) Co morbid cond: 10 (15.4%)	33 (84.6%) 6 (15.4%)	22 (84.6%) 4 (15.4%)	0.631
Occupation	Nil job: 11 (16.9%) Working: 54 (83.1%)	7 (17.9%) 32 (82.1%)	4 (15.4%) 22 (84.6%)	1.00
Other medication	No other med: 18 (27.7%) Other medication: 47 (72.3%)	13 (33.3%) 26 (66.7%)	5 (19.2%) 21 (88.8%)	0.266

The above table shows that there was no statistical significance difference between normal BMD group and abnormal BMD group in terms of gender, occupation, Axis I diagnosis, exposure to other antipsychotic medications in the past and other co-morbid conditions.

Table 6: Bio chemical parameters compared for BMD at the neck of the femur

Variables	Mean with SD	Normal BMD N =39	Osteoporosis/penia N=26	P value
Prolactine level	46.73 (32.51)	43.67 (31.13)	49.74 (33.90)	0.460
Serum calcium	8.57 (0.315)	8.64 (0.32)	8.51 (0.31)	0.119
Vitamin D	15.18 (8.19)	16.83 (9.23)	13.54 (0.15)	0.133
Serum alkaline phosphatase	83.06 (50.25)	81.43 (21.08)	84.69 (29.17)	0.603
Serum Phosphorous	3.66 (0.52)	3.86 (0.55)	3.46 (0.48)	0.004

On comparison, the biochemical parameters in normal BMD and abnormal BMD group did not show significant difference. The biochemical parameters checked were Serum Prolactine, Calcium, Phosphorous, Vitamin D and serum Alk phosphatase.

Table 7: Prolactine value compared across the abnormal and normal BMD groups at femur neck

Variable	N=65	Abnormal BMD N=26 in neck of the femur	Normal BMD N=39 in neck of the femur	P value	Odd ratio with CI with risk
Hyperprolactinemia	53 (81.5%)	23 (88.5%)	30 (76.9%)	0.334	2.3 (0.559-9.468)
Normal	12 (18.5%)	03 (11.5%)	09 (23.1%)		
Vitamin D deficiency	20 (32.3%)	9 (34.6%)	11 (30.6%)	0.736	0.831 (0.284 - 2.43)
Normal/insufficient Vitamin D level	42(67.7%)	17 (65.4%)	25 (69.4%)		

Comparative analysis between the subject with normal BMD and abnormal BMD group at femur neck in respect to hyperprolactinemia and serum vitamin levels did not yield significant difference.

Bone mineral density measure in Lumbar spine

29 (44.7%) subjects had BMD abnormalities in the lumbar spine. 9(13.8%) had osteoporosis, and 20(30.9%) had osteopenia. Of the 9 with osteoporosis, 7 were men and 2 were women.

Table 8: Demographic and Clinical parameters compared for lumbar spine

Variables	N (%)	Normal BMD N =36	Osteoporosis/ penia N=29	P value	OR CI
Gender	Female: 32 (49.2%) Male: 33 (50.8%)	20 (62.5%) 15 (46.9%)	12 (37.5%) 17 (53.2%)	0.315	0.529 (0.195-1.435)
Diagnosis of the patient	Schizophrenia: 38 (58.5%) BPAD/SA disorder: 27 (41.6%)	21 (56.8%) 14 (51.9%)	16 (43.2%) 13 (48.1%)	0.697	0.821 (0.303-2.22)
Religion	Hindu Others	31(51.7%) 4 (100.0%)	29 (48.3%) 0	0.060	0.51 (0.40-0.66)
Co-morbid axis I diag.	No Co morbid disorder: 55 (84.6 %) Co morbid conditions: 10 (15.4%)	27 (50.0%) 08 (80%)	27 (50.0%) 02(20.%)	0.080	4 (0.77-20.59)
Occupation	Nil job: 11 (16.9%) Working: 54 (83.1%)	6 (54.5%) 29 (54.5%)	5 (45.4%) 24 (45.4%)	0.992	1.007 (0.27-3.71)
Other medication	No other med: 18 (27.7%) Other medication: 47 (72.3%)	09(50.0%) 26(56.7%)	09 (50.0%) 20 (43.3%)	0.637	1.3 (0.436-3.87)

Table 8 looks at the differences between the normal BMD group and the osteopenic/ osteoporotic group in terms of gender, remove makes no sense, occupation, Axis I diagnosis exposure of other antipsychotic medication in the past and other co morbid conditions. No statistical difference was seen.

Table 9: Bio chemical parameters compared for lumbar spine

Variables	Mean with SD	Normal BMD N =34	Osteoporosis /penia N=29	P value
Prolactine level	46.73 (32.51)	49.30 (31.93)	43.15 (33.83)	0.460
Serum calcium	8.57 (0.315)	8.60 (0.35)	8.58 (0.29)	0.826
Vitamin D	15.18 (8.19)	16.59 (8.32)	14.27 (8.87)	0.295
Serum alkaline posphatase	80.28 (19.18)	81.43 (21.08)	85.58 (30.10)	0.396

Comparative analysis between the subject with normal BMD and abnormal BMD group at spine in respect to serum prolactine, calcium, Vitamin D, serum Alk phosphatase did not yield significant difference.

Table 10: serum prolactin and vitamin D levels compared across the abnormal and normal BMD groups

Variables	N=65	Abnormal BMD N=26 spine	Normal BMD N=39 in neck of the femur	P value	Odd ratio with CI with risk
Hyperprolactinemia	52 (81.5%)	23 (44.2%)	29 (55.8%)	0.790	0.79(0.226-2.788)
Normal	12 (18.5%)	06 (50.0%)	06 (50.0%)		
Vitamin D deficient group	20 (32.8%)	10 (35.7%)	10 (30.3%)	0.654	0.783 (0.268 - 2.286)
Vitamin D non-deficient	41 (67.2%)	18 (64.3%)	23 (69.7%)		

Comparative analysis between the subject with normal BMD and abnormal BMD group at spine in respect to hyperprolactinemia and serum vitamin levels did not yield significant difference.

Prevalence of gonadal dysfunction

Of the 65 subjects, 22 (33.8%) had either amenorrhea or erectile dysfunction. 8 of 33 females (24.2%) reported amenorrhea and 14 of 32 males (43.8) had erectile dysfunction.

On comparing report of either erectile dysfunction or amenorrhea with bone mineral density changes at lumbar spine, a statistically significant difference was seen. The odds ratio was 3.71 with CI of 1.23-11.24.

Table 11: sexual dysfunction compared in both normal and abnormal BMD at lumbar spine

Variable	Sub groups	Normal BMD spine	Abnormal BMD spine	P value	OR
ED/amenorrhea	Yes: 21(32.8%) No: 43(67.2%)	7 (33.3%) 28 (65.1%)	14 (66.6%) 15 (34.9%)	0.016	3.71 (1.23-11.24)
Amen. in female	Yes: 8 (25.0%) No: 24 (75.0%)	4 (50.0%) 16 (66.7%)	4 (50.0%) 8 (33.3%)	0.399	2.0 (0.39-10.156)
ED in male	Yes: 13 (40.6%) No: 19 (60.4%)	3 (23.1%) 12 (63.2%)	10(6.9%) 7 (36.8%)	0.026	5.71 (1.16-28.07)

A sub group analysis across gender groups in relation to BMD changes at spine was carried out.

Lowered BMD did not correlate with amenorrhea in women p=0.399 and OR 2.0 (CI: 394-10.156).

Among men, ED is significantly related to BMD changes at lumbar spine p 0.026 and OR 5.71(1.16-28.07)

Serum Vitamin D and relationship with other factors:

Table 12: deficient and non deficient vitamin level compared across other variables

Variables	Sub groups	Normal/insuf Vit. D	Vitamin D deficient	P value	OR CI
Gender	Male 31(50%) Female 31 (50%)	18(58.1%) 24(77.4%)	13 (41.9%) 07 (22.6%)	0.103	2.47 (0.821-7.46)
BMI	Normal 27 (53.4%) Over weight / obesity 31(46.6%)	19 (70.4%) 21 (67.7%)	08 (29.6%) 10 (32.3%)	0.829	1.13(0.37-3.46)
ED /Ame-norrhea	No 40 (64.5%) Yes 22 (35.5%)	29 (72.5%) 13 (59.1%)	11 (27.5%) 09 (40.9%)	0.280	0.55(0.18-1.64)
Dose of Risperidone	2-4mg 4.5-10mg	26(78.8%) 16(55.2%)	07(21.2%) 13(44.8%)	0.047	3.01(0.99-9.157)
BMD in spine	Normal BMD Abnormal BMD	23 (69.7%) 18 (64.3%)	10 (30.3%) 10 (35.7%)	0.786	0.783 (2.68-2.28)
BMD in neck	Abnormal BMD Normal BMD	17(65.4%) 25(69.4%)	09 (34.6%) 11(30.6%)	0.736	0.83(0.28-2.43)

Of the 65 subjects, 90.8% had abnormal serum vitamin D levels. In accordance with the WHO guideline, 20(30%) had Vitamin D deficiency and 40(60.8%) had vitamin D insufficiency and 3(4.1%) had vitamin D sufficiency.

For analysis, they were divided into deficient and not deficient groups. In males the prevalence of vitamin D deficiency was 13(41.9%) and in females it was 7 (22.6%). No statistical difference was seen when vitamin D deficient group and vitamin D non-deficient group were compared on the basis of gender, body mass index, erectile dysfunction/amenorrhea and abnormal BMD changes in spine and femur neck. However, the group on higher dose of Risperidone (>4 mg per day) showed higher risk of developing Vitamin D deficiency with a p value of.047 OR 3.01(.99-9.157) in comparison to the group receiving.

DISCUSSION

Antipsychotic medication and BMD changes

Our data showed that 60% of patients on Risperidone have low bone mineral density (osteopenia or osteoporosis). Out of 10 people who have osteoporosis, 80% are males and 20% are females. The remaining 23 have osteopenia. This is a high prevalence, given the mean age (29.6years, SD 6.56) and the fact that these are ambulatory patients, with the majority having some form of productive occupation.

The prevalence found by our study is similar to the finding of the other studies, in non-Indian populations.

In a study on psychiatric in-patients, bone mineral density in the lumbar spine and in the femoral neck showed that significant numbers of patients, especially male patients, had a remarkable decrease in bone mineral density when compared with age- and sex-matched normal data. These results may be related to low levels of gonadal hormones, especially in male subjects (Halbreich et al). Wyszogrodzka et al demonstrated that patients with schizophrenia suffered from a lower mean bone mineral density in comparison to the control group. However, both these studies were conducted on inpatients on a psychiatric ward. There is no data on Indian patients.

The normative standard used is based on Caucasian data, as there is limited Indian normative data. Indian adult population has been found to have low bone mineral density. In a study on healthy army recruits, with mean age of 25 years, Tandon showed

that 35-50 % of the men (N=20) and 14-32% women (N=22) had BMD abnormalities with an additional 10% of men having osteoporosis of the lumbar spine.

It is possible that normative data derived from Caucasian populations is inapplicable in our population, leading to an overestimate of BMD deficiency in our study population. Unfortunately, there are no established norms for BMD in healthy Indians.

Hyperprolactemia and BMD changes

88.5% of our subjects who had decreased BMD at either neck of femur or lumbar spine, or both, had hyperprolactinemia.

Our study also showed an inverse relationship between prolactin level and BMC (bone mineral content) at neck of the femur.

Abraham et al. (2003) reported an inverse relationship between prolactin level and bone mass in patients receiving antipsychotic medications. Other studies (Hummer et al, 2005; Halbreich et al, 1995) have found a similar relationship. However, these have been looked at as continuous variables, without categorization into hyper or hypoprolactinemic states.

Thus patients on prolactin raising antipsychotic medication need to be screened for hyperprolactinemia and other factors, which can decrease BMD. Patients with hyperprolactinemia should be investigated further in order to monitor BMD changes.

Antipsychotic induced hyperprolactinemia

In our study, 84% of women and 78.8% of men, have hyperprolactinemia. In a recent study approximately 60% of women and 40% of men treated with a prolactin-raising antipsychotic had a prolactin level above the upper limit of the normal range (Haddad and Wieck, 2004). Our finding of hyperprolactinemia in female is comparable to the findings of the other studies. But, in males prevalence of hyperprolactinemia is almost double that in available literature. Such a high prevalence of hyperprolactinemia in Indian male psychiatric population needs to be further researched.

81% subjects had hyperprolactinemia, This is similar to that of Wong et al, 2007, who found out that patients on Risperidone had the highest level of plasma prolactin, as compared to those on typical antipsychotic medication.

Those with hyperprolactinemia did not differ from the non-prolactin raised group in clinical parameters and the other biochemical factors measured.

Hyperprolactinemia is an adverse effect of antipsychotic medication that has been underinvestigated by clinicians and researchers. Risperidone, in comparison to other atypicals commonly used, is more likely to cause hyperprolactinemia. This effect needs to taken seriously and investigated further.

No published data is available so far for the Indian population.

Antipsychotic induced menstrual irregularities and hyperprolactinemia

Sixty percent of women subjects, with a mean age of 30 years, had menstrual related abnormalities. 24% had amenorrhea and 38% had delayed menstruation. All women who developed amenorrhea had hyperprolactinemia.

Existing data suggests that irregular cycles and galactorrhoea are common, but that clinicians underestimate the prevalence. For example, well conducted studies of women treated with conventional antipsychotics have reported prevalence rates of approximately 45% for oligomenorrhoea / amenorrhea and 19% for galactorrhoea.

An illness-related under-function of the hypothalamic-pituitary-gonadal axis in female patients with schizophrenia may also contribute to menstrual irregularities.

Also, there is evidence in literature to show that baseline menstrual problems get worsened and that galactorrhea or gynecomastia manifest only after exposure to antipsychotic medication (Kohen et al, 2008).

However we did not elicit information regarding galactorrhea. This must be done in future studies.

Biller et al showed that the duration of amenorrhea was positively associated with severity of BMD loss. Biller et al., 1991 showed that forty-two percent of hyperprolactinemic women who remained amenorrhic for a period of 1.7(SD 0.2) years exhibited BMD loss more than two standard deviations below the control mean.

Hyperprolactinemic hypogonadal women with secondary amenorrhea resulting from low estrogen production were found to have significantly lower BMD than hyperprolactinemia women who maintained sufficient estrogen levels to retain menses.

This suggests that women on Risperidone, who develop amenorrhea, are at high risk for lowered BMD and possibly for fractures.

The present study has not assessed the duration of amenorrhea and its relation ship with changes in BMD

Sexual dysfunction and antipsychotic medication

Forty four percent of males with mean age of 28.84 (6.59) reported erectile dysfunction In a study by Ghadirian *et al* (1982), among out-patients with schizophrenia, 54% of men and 30% of women reported sexual dysfunction. Under reporting of sexual dysfunction in our study is possible. Reasons include lack of extensive questionnaire, culture specific factors and stigma related issues.

Studies show that psychiatric patients rated drug-induced sexual dysfunction as more 'bothersome' than most psychiatric symptoms of their illness (Finn *et al*, 1990).

Knegtering et al reported a study to comparing sexual side effects of prolactin rising antipsychotic medication with those on non-prolactin rising ones. Results showed that prolactin raising antipsychotic induced sexual side effects were significantly more as compared to prolactin sparing antipsychotic medication. (Knegtering et al, 2008).

The presence of ED was significantly associated with impairment in BMD. The report of ED should alert the clinician to evaluate BMD.

Vitamin D and chronic mental illness

Our study on patients with on long term Risperidone showed that more than 90 % had either vitamin deficiency or insufficiency. 30% were deficient in Vitamin D (<10 ng/mL). It is alarming to note that 30% of ambulatory psychotic out patients in their maintenance phase of treatment, with a mean age of 30 had significant vitamin D deficiency. Vitamin D deficient patients received a significantly higher dose of Risperidone, and this association has to be studied in larger sample size.

A few studies have evaluated the magnitude of vitamin D deficiency in patients on long-term antipsychotic medication.

Tiangga E et al has studied the prevalence of vitamin D deficiency in a group of male psychiatric in-patients and observed that vitamin D deficiency was mostly associated with black and minority ethnic background suggesting that that the psychiatric patients may be at risk for Vitamin D deficiency. Poor nutrition and reduced duration of exposure to sunlight have been postulated as possible mechanisms responsible for a vitamin D3 deficiency in patients with schizophrenia.

Vitamin D therapy is recommended clinical practice in patients suffering from a decrease of bone mineral density. It is cheap, easily available and dosing regimen is simple.

Our finding of a relationship between low vitamin D levels and reduced bone mineral density resulted from an exploratory analysis and therefore needs to be replicated with prior hypothesis testing

It raises the possibility that prophylactic addition of vitamin D to the treatment of patients with antipsychotics could reduce the risk of loss of bone mineral density.

STRENGTHS

1. Risperidone is a widely used antipsychotic. Schizophrenia and other chronic psychoses are conditions that manifest in early adulthood, and often need life long maintenance treatment. There is no Indian data on the effect on bone mineral density, its long-term consequences and its management.

2. Sample size was calculated based on an a priori hypothesis.

3. Multiple factors involving the outcomes of interest were assessed in order to reduce bias through confounders.

4. The study addresses a clinically relevant issue.

5. DXA scans are expensive. The facility for this test is not easily available. Significantly lowered BMD values correlate with reports of erectile dysfunction in men. In a resource poor setting, this clinical information has potential as a screening measure to identify those at greater risk for osteopenia or osteoporosis.

LIMITATIONS

1. There was no matched healthy adult control group for comparison of parameters measured.

2. Study subjects had heterogeneous diagnoses.

3. Other factors influencing Vitamin D levels, such as extent of direct sun light exposure, levels of physical activity and dietary habits of our subjects, were not assessed.

4. Sexual dysfunction is a sensitive area for assessment. Given the cross sectional nature of the study, and the gender of the investigator, this area were assessed only in men.

CONCLUSION

1. This hospital based study of patients receiving maintenance Risperidone for a minimum of one year showed a 50% prevalence of abnormal bone mineral density. 10 (15.4 %) had osteoporosis, and 23 (35.4%) had ostepenia. The mean age was only 29.4 (6.56) years.

2. Sixty percent of women had menstrual irregularities and all women with amenorrhea were hyperprolactinemic.

3. 44% of the men reported erectile dysfunction. ED was more significantly associated with changes in BMD.

4. Thirty percent of the subjects had severe vitamin D deficiency. The direction of causality, if any, and its possible therapeutic potential to reverse or delay this process, remains to be explored.

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INFORMATION FORM

Dear Patient,

I am Dr Jayaprakash and I am doing a study. This study is about side effects of the medicine that your doctor is prescribing for you – Risperidone. All medicines have side effects, and some studies abroad have shown that Risperidone may cause some weakness in the bones, similar to what happens in older age. We do not know if this happens in Indian patients. I would like to get some knowledge about this. To do this I need to test people like yourself – who have an illness and have to take this medicine.

To do this I need to ask you some questions about your health and body activities, illness and treatment. Whatever you tell me will be kept anonymous and confidential.

To study the bones, a special scan has to be done. The scan machine is in CMC hospital. If you agree to taking part in the study, I will make an appointment for this test. You will not be asked to pay anything. On the day of the exam you may eat normally. You must reach the scan department 15 minutes before the schedule time. The procedure will take around 20 minutes. No anesthesia, medicine or injection is required. This scan is called DEXA bone densitometry.

During the scan X-ray will be used to take a picture of the bone. Rays used are less than one-tenth the dose of a standard chest X-ray. The amount of radiation used is extremely small—less than one-tenth the dose of a standard chest x-ray. Large amounts of radiation can harm the body. To the best of our knowledge, the radiation given in the scan is unlikely to harm you.

This test will tell us if your bones are weak.

We will be doing some of the blood tests, which we usually do not do regularly. For this study we would be doing these fasting blood tests for better understanding of the factors related to weakness in the bones if at all present.

You are invited to be part of this study. We will give you a copy of this information for you to keep. I will be happy to answer any doubts or questions you have.

Taking part in this study will not affect your treatment in any way. If you do not wish to take part, you will continue with treatment as usual. Even if you agree to take part, you can change your mind at any time and leave the study. This will not affect your treatment in any way.

If you wish to take part, I will ask you to sign a form, saying that I have explained all the details to you and that you are willing to take part. Even after signing, you may change your mind and cancel it at any time.

The research committee and the ethics committee of the Christian Medical College, Vellore, have approved this study. This means that a group of doctors of this hospital have studied this plan and have given permission for me to do this study.

If you have any doubts, or want additional information, contact any of the following in this hospital. We can be contacted at the following address:

*Dr.JP Russell Ravan	Dr.Naveen Thomas	Dr.Deepa Braganza
Registrar	Assistant Professor	Professor

Dept. of Psychiatry
Christian Medical College
Bagayam,Vellore-632 002.
Tamilnadu

CONSENT FORM

Dr Jayaprakash has explained to me in detail about the study and risks involve secondary to radiation during DEXA Scan and blood tests. I understand that taking part may not benefit me directly. My treatment will not be affected if I refuse to participate in the study. I can withdraw consent at any point without having to say why.

I, ……., hereby consent to participate in the study.

Date……

Name …….

APPENDIX II

Clinical Data sheet

Date of Assessment……

Socio demographic profile

Hospital Number ……

Age ……

Gender …….. ……

Marital Status ……

Religion ……

Whether patient is employed ……..……...

Height……Weight……

Disease and Diagnostic profile

ICD 10 Diagnosis ……

Co-morbid Axis I Diagnosis …….

Substance abuse …….

Any co-morbid medical condition ……..

Other medication taken with Risperidone ……. …….

Age at which illness began ……..……

Dose of Risperidone …….

Duration of untreated psychosis …….

Duration of treatment with Risperidone …….

Is there any expose to other antipsychotic treatment ……. If yes

Name and duration of other antipsychotic drug……

Sexual or menstrual functioning profile

Base line sexual functioning ……..

Sexual dysfunction on treatment Y/ N Duration

If yes, Loss of Libido / ED/ PME …….

Menstrual function before onset of illness ……

Menstrual function before commencement of Risperidon ……..

Period of amenorrhea on Risperidone ……

Height ……..

Weight ……..

Circumference at the level of umbilicus ……..

Whether the patient can stand unsupported from squatting position ……